REMARKS

Claims 43 to 47, 50, and 53 to 140 are pending in the application. Claims 79 to 88 were withdrawn previously by the Examiner as directed to a non-elected invention. Applicants have canceled claim 42 and have added new claims 121 to 140. New claims 121 to 140 are supported throughout the application, e.g., by canceled claim 42 and previously presented claims 53 to 56. Applicants have amended the specification to correct various informalities and to replace Figures 2, 9 and 11 as requested by the Examiner. The amendments add no new matter to this application.

Inventorship

Applicants acknowledge that the inventorship of this application has been changed properly to "Augustine M.K. Choi and Leo E. Otterbein."

Withdrawn Rejections

While the examiner did not explicitly withdraw many of the previous rejections, applicants assume that all prior rejections not reasserted in the present Office Action are withdrawn. Thus, applicants acknowledge the withdrawal of the following rejections:

(a) the rejection of claims 65, 66 and 68 for an alleged lack of enablement;

(b) the rejection of claims 65 to 69, 74 and 89 as allegedly indefinite for not reciting the term "therapeutically effective amount";

(c) the rejection of claim 65 as allegedly indefinite for lack of antecedent basis for the phrase "reduce or prevent inflammation";

(d) the rejection of claim 61 as allegedly anticipated by and/or obvious in view Campbell (*Brit. J. Exp. Path.*, 15(5):287-294 (1934)); and

(e) the provisional rejection of claims 57 to 59 and 62 to 65 as allegedly anticipated by Chapman et al. (Am. J. Resp. Crit. Care Med. 159(3):A218 (1999).

Objections to the Specification

The Office Action objected to the specification for various informalities. Applicants have amended the specification as suggested in the Office Action and request that these objections be withdrawn.

The Office Action also objected to claims 53 to 55, 98, 99, 102 to 104, 106, 108, 110, 112 to 114, 118 and 120 as depending from a rejected base claim. In view of the arguments presented below, the base claims should be allowed, thereby obviating this objection. Accordingly, applicants request that the objection to the claims be withdrawn.

Rejections under 35 U.S.C. § 112, first paragraph

The Office Action reinstated the rejection of claims 42 to 47, 50, 56 to 78, 89 to 97, 100, 101, 105, 107, 109, 111, 115 to 117 and 119 as allegedly not enabled. For reasons unrelated to this rejection, applicants have canceled claim 42 thus obviating this rejection with regard to that claim. Applicants respectfully traverse this rejection and submit that the claims are fully enabled by the specification as filed for the reasons discussed below.

As an initial matter, in reinstating the rejection, the Office Action restates the reasons for rejection that were first set forth in the Office Action dated July 30, 2002 (at pages 2 to 4). Applicants submit that they fully addressed all of these points in their official Response filed January 30, 2003 and, therefore, incorporate those arguments herein by reference in their entirety. Applicants' additional reasons for traversal are provided below.

The present Office Action states (at page 6):

> Although Applicant has provided evidence that inhalation of carbon monoxide can treat or reduce inflammation as specifically set forth in the claims indicated above, Applicant has not shown how carbon monoxide can be effectively administered in other forms. Applicant has argued that modes of administration of gases to patients other than by inhalation are known in the art. However, none of the references cited involve the use of carbon monoxide and even if the references cited were sufficient to enable one to administer carbon monoxide, Applicant has not shown that other forms of administration would be effective in treating the various conditions or disease states.

Applicants respectfully disagree and submit that the specification provides information sufficient to enable a skilled practitioner to practice the invention using modes of carbon monoxide (CO) administration other than inhalation.

In previous communications with the Office, applicants pointed out that the specification provides a detailed explanation of how CO can be used to treat oxidative stress and inflammatory disorders. It also sets forth working examples in art-recognized models. At the time the application was filed, physicians fully appreciated that gaseous compositions in general could be administered to patients in any number of ways. For example, at the time the application was filed, it was known that nitric oxide (NO) gas or CO gas could be administered to patients using an extracorporeal membrane oxygenator (ECMO) apparatus, a cardiopulmonary bypass (CPB) apparatus, or an intravenous oxygenator (IVOX) (see, e.g., Head et al., U.S. Patent No. 5,885,621, column 4, lines 41 to 50; designated as "AC" on the Information Disclosure Statement (IDS) form PTO-1449 filed on March 25, 2003). These are merely alternative means for introducing gases into a patient's bloodstream, typically used when the patient's lungs are not functioning properly and so the therapeutic gas cannot be delivered effectively by inhalation. Regardless of whether it reaches the bloodstream through the lungs or through a non-inhalation mode, once the CO is in the bloodstream, it would be expected to treat the underlying condition.

In using an *in vivo* model where CO was administered by inhalation and its systemic anti-inflammatory effects were observed, applicants sought to demonstrate that systemic CO administration in general has positive effects, not simply that inhaled CO has those effects. Applicants therefore acknowledge the Office Action's statement that applicants "have provided evidence that inhalation of carbon monoxide can treat or reduce inflammation as specifically set forth in the claims indicated above[.]" Knowing about all of the other effective modes of gas administration that existed, skilled practitioners would have also accepted applicants' model of CO inhalation as demonstrating the effectiveness of CO administered using any of those other modes. The Office Action cites no evidence to the contrary.

Given that (1) applicants' CO inhalation model was accepted by skilled practitioners, and (2) the specification is enabling for treatment by inhalation, skilled practitioners would clearly

have been enabled to treat animals using non-inhalation modes, e.g., ECMO, CPB or IVOX. Despite this, the Office Action appears to suggest that every mode of administration covered by the claims would have to be used in a working example in order to provide enablement for treatment using those modes. Such a showing is, of course, not required by law.

In attempting to rebut applicants' previous arguments for enablement, the Office Action quotes from applicants' previous arguments made in the context of establishing non-obviousness over Eschwey (WO 98/08523; see applicants' Response filed January 30, 2003). Applicants also cited Eschwey when responding to the present rejection in applicants' most recent response (see applicants' Response filed November 10, 2003) as evidence that many different modes of gas administration were known at the time the present application was filed. The Office Action states (at page 6):

> Applicant has argued with respect to Eschwey, which Applicant cites as a reference showing other forms of administration, "[g]iven that Eschewey's complete lack of guidance regarding the biological activities and uses of carbon monoxide, and the generally known harmful effects of carbon monoxide at high concentrations, a skilled practitioner would have had no reason to expect such treatment to be successful".

The Office Action appears to quote this statement (found in applicants' Response filed January 30, 2003 at page 19, lines 3 to 6) to suggest that applicants have somehow implicitly acknowledged that skilled practitioners had insufficient guidance, at the time the application was filed, to administer CO using modes other than inhalation. Applicants have in no way done so. Applicants fail to see how this statement could conceivably be construed as anything other than a conclusion to applicant's argument that Eschwey, as alleged prior art, does not provide skilled practitioners with a motivation to treat animals with CO, nor a reasonable expectation of success in doing so. At no point did applicants state or imply that practitioners lacked the skill or ability to administer gases (such as CO) to patients using modes other than inhalation. Indeed, applicants clearly would have been mistaken in doing so, given Eschwey's recitation of many different modalities for gas administration that were known at that time.

In view of the above, applicants submit that limiting the claims to delivery of CO by inhalation is not warranted, and request that the rejection based on that ground be withdrawn.

The Office Action also states, presumably with respect to enablement of claims explicitly reciting methods of treating cancer (i.e., claims 60, 61, 90 to 95, 100, 101, 116 and 117):

> Applicant has argued that retardation of growth was not sufficient to have taught a clinically useful approach to treating cancer (Remarks (11/21/2003, pgs. 19,20).

This is simply incorrect. At no point in their Response filed November 19, 2003 (or at any other point) did applicants make anything resembling such a statement. Rather, applicants pointed out that Maxwell (*J. Pharmacol.*, 49:270-282 (1933) is replete with negative statements about the dire effects of CO administration on the body, e.g., severe anoxia, weakness and prostration, etc.). Applicants asserted that Maxwell, in making those negative statements, provided no motivation to skilled practitioners to use CO as a therapeutic agent for treating cancer, nor a reasonable expectation of success in doing so. Applicants asserted that Maxwell would in fact have dissuaded skilled practitioners from using CO as a therapeutic agent to treat cancer. Finally, applicants asserted (at page 20, lines 1 and 2 of the Response filed November 19, 2003):

> Given such statements, Maxwell can't be said to have taught a clinically useful approach to treating cancer.

Applicants' statements regarding Maxwell cannot properly be construed to be an argument that "retardation of growth was not sufficient to have taught a clinically useful approach to treating cancer." Maxwell, viewed as a whole, taught much more than retardation of growth - he taught that in order to achieve retardation of tumor growth, one would need to administer a level of CO high enough to induce anoxia (page 271, lines 12 to 15). Applicants were making the point that only after reading the present application would a skilled practitioner have a motivation and reasonable expectation of success in using CO as a therapeutic agent. This is, in part, because applicants' specification explicitly teaches that CO can be administered for the purpose of treating cancer. The specification provides a list of exemplary types of cancer that can be treated with CO and provides a detailed description of how to safely and effectively

administer CO as a therapeutic agent without the severe side effects noted by Maxwell. This is guidance that is clearly not provided in Maxwell, who says he tested CO in the first place because of its ability to induce severe anoxia, and nowhere suggests that CO inhalation could be a useful means to treat cancer.

Further, as is acknowledged in the Office Action, applicants provided the Office with direct evidence that the claimed methods work in their Response filed January 30, 2003. Applicants submitted this evidence at the Examiner's request and in support of their arguments that the claims were fully enabled at the time of filing. Specifically, applicants guided the Office to applicants' Provisional Application Serial No. 60/386,561, which provides data demonstrating that animals injected with tumor cells and exposed to appropriate doses of CO had increased survival rates, exhibited reduced tumor growth and exhibited reduced angiogenesis (which is often an important pathologic component in cancer). This is clearly much more evidence than what the Office Action gives applicants credit for when it states (at page 7, lines 1 and 2):

> The only evidence provided by Applicant was from Application Serial No. 60/386,561 which only shows a reduction of tumor growth.

Thus, applicants reiterate that their claims that explicitly recite methods of treating cancer (i.e., claims 60, 61, 90 to 95, 100, 101, 116 and 117) are fully enabled by the specification as filed. At no point in their prior responses did applicants state or imply that a practitioner lacked the ability or skill to administer CO to patients to treat cancer at the time the application was filed, or that "retardation of growth was not sufficient to have taught a clinically useful approach to treating cancer." Applicants respectfully submit that the Office has set forth no proper legal basis upon which to reject the claims as lacking enablement.

For the reasons discussed above, applicants submit that all of the claims are fully enabled by the specification as filed. Given the information and examples provided in the specification, a skilled artisan would not need to engage in undue experimentation to make or use the claimed invention across its full scope. The Office Action cites no evidence to contradict this assertion.

Thus, applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 42 to 47, 50, 53 to 78, 89 to 97, 105, 107, 109, 111, 115, 117 and 119 were rejected under 35 U.S.C. § 112, second paragraph for allegedly failing to set forth the subject matter that applicants regard as their invention. For reasons unrelated to this rejection, applicants have canceled claim 42 thus obviating this rejection with regard to that claim. Applicants respectfully traverse this rejection for the reasons discussed below.

In maintaining this rejection, the Office Action first restates its reasons for rejection set forth in the Office Action dated May 19, 2003 (at pages 2 to 4). Taking the position that the claims should be limited to delivery of CO via inhalation, the Office Action quotes from applicants' Response filed January 30, 2003: "none of the publications cited in the Office Action, singly or in combination, teaches or suggests administering inhaled carbon monoxide gas as a therapeutic agent to treat the diseases and conditions recited in the pending claims," and says that this indicates that the invention is limited to CO delivered via inhalation. As an initial matter, applicants submit that they fully addressed this point in their official Response filed November 19, 2003, and therefore incorporate those arguments herein by reference in their entirety.

Applicants respectfully submit that it is improper for the Office to select certain of applicants' statements, quote them in a different context and then assert that they are an implicit acknowledgement that the invention is limited to administration of CO by inhalation. Applicants were making the point that the prior art did not disclose the use of CO (inhaled or otherwise) as a therapeutic agent to treat the diseases and conditions recited in the claims. Saying that the prior art does not disclose a particular embodiment is not equivalent to saying that the claims are limited to such an embodiment. The specification does not limit the invention to inhalation of CO, and the fact that applicants claimed administration by inhalation in several dependent claims proves that applicants regarded inhalation to be only one embodiment of the present invention.

With all due respect, the Office has set forth no proper legal basis for requiring that the independent claims be limited to inhalation.

Further, applicants respectfully point out that their Response filed January 30, 2003, made several statements at many other points about CO administration that did not recite the word "inhaled." The Office Action simply ignores these. Exemplary excerpts include:

- As would any skilled practitioner, applicants used these models to demonstrate the effectiveness of carbon monoxide treatment *in vivo*. (Page 7)

- As amended, these claims recite administering to a patient a "therapeutically effective amount" of a composition comprising carbon monoxide. (Page 17)

- During the Telephonic Interview, applicants' representative asserted, and Examiner Choi confirmed, that Abidin does not teach, or even suggest, administering carbon monoxide to humans (or any other animals) as a therapeutic agent for any purpose. (Page 17)

- Accordingly, a skilled practitioner would not have been motivated by Eschwey to administer carbon monoxide gas to treat the diseases and conditions recited in applicants' claims. (Page 19)

- Nowhere does Choi teach, or even suggest, that exogenously-delivered carbon monoxide could be used as a therapeutic agent. (Page 19)

- Abidin does not teach, or even suggest, that carbon monoxide gas could be administered as a therapeutic agent to treat any of the diseases or conditions recited in applicants' claims. (Page 20)

Given the many statements that do not recite the word "inhaled," and that were made in response to rejections under 35 U.S.C. §§ 112, 102 and 103, applicants fail to see why the Office has selected for special focus applicants' statements that do recite the word "inhaled," or why the latter statements should be considered of any greater importance than the former statements in determining what applicants believe to be their invention. Applicants submit that it is improper for the Office deem the invention limited to administration by inhalation based on this selective focus.

Furthermore, applicants take issue with the following statement in the Office Action (at page 7):

> Applicant argues that the quote was taken out of context, however, Applicant also argued in the response with respect to the 112 rejection that the Specification enables the treatment of various diseases/conditions with inhaled oxygen [sic]. Applicant's argument regarding the fact that it set forth inhalation in the dependent claims does not overcome the rejection. Applicant knew of the said amendment, yet made the statements nonetheless.

While it is true that applicants used the word "inhaled" at several point in their response to the rejection under 35 U.S.C. § 112, first paragraph, this was appropriate given the issues raised in the Office Action. For example, in setting forth the rejection, the Office Action stated (at page 3, lines 3 to 6; emphasis added):

> Also, it appears that the active compounds are *inhaled*, however, other than the lungs there does not appear to be set forth in the disclosure how the compounds, in therapeutically effective amounts, reach the intended site be it kidneys, brain, heart, liver, spleen, skin, or systemically in general.

Accordingly, applicants responded, for example, by pointing out that the specification itself provides direct evidence that inhaled CO has system-wide effects. Thus, given that the Office Action explicitly called for a discussion about inhaled CO, applicants fail to see how the fact they recited the word "inhaled" at numerous points in their response supports the Office's subsequent argument that the claims should be limited to administration by inhalation. Applicants respectfully submit that it does not support the Office's argument.

Applicants also take issue with the Office Action's assertion (at page 7) that:

> Applicant's argument regarding the fact that it set forth inhalation in the dependent claims does not overcome the rejection. Applicant knew of the said amendment, yet made the statements nonetheless.

Again, the Office Action appears to assert that applicants, having made those statements, somehow acknowledged that the claims should be limited to inhalation. Applicants have by no means done so. Applicants of course agree that they made those statements, but reiterate that they are no more or less important than the statements that do not recite the word "inhalation" or

"inhaled." Applicants maintain that they have at all times regarded inhalation to be only one embodiment of the present invention.

For the reasons above, applicants submit that the claims correspond in scope with what they regard as the invention, and that they are therefore in full compliance with 35 U.S.C. § 112, second paragraph. Even if applicants' prior discussion of one embodiment of the invention confused the Examiner about the full scope of the invention, applicants have now clearly dispelled that confusion. The claims particularly point out and distinctly claim the present invention as required under the statute. Thus, applicants respectfully request that the present rejection be reconsidered and withdrawn.

Rejections Under 35 U.S.C. §§ 102 (a), 102 (g) and 103

Claims 42 to 47, 50, 53, 62, 65, 67, 104 and 108 were rejected under 35 U.S.C. §102 (a) as allegedly anticipated by or, in the alternative, under 35 U.S.C. §103 (a) as allegedly obvious over Otterbein et al. (American Journal of Respiratory and Critical Care Medicine, volume 159, No. 3, Supp., pp. A218 (March 1999); hereinafter "the Otterbein abstract"). As an initial matter, applicants have canceled claim 42, thus obviating this rejection with regard to that claim. Claims 43 to 47 and 50 have been amended to be independent. Claim 53 has been amended to depend from amended claim 43.

Applicants submit that the Otterbein publication is not prior art citable against at least claims 43, 50, 53, 62, 65, 67, 104 and 108. The present application claims priority from U.S. Application Serial No. 09/538,788, which has a filing date of March 30, 2000, and from Provisional Application Serial No. 60/127,616, filed on April 1, 1999. Claims 43, 50, 53, 62, 65, 67, 104 and 108 are supported by the disclosure of the provisional application, e.g., at the first page of the application, at lines 2 to 4 and 34 to 36, at the fourteenth page (labeled as page 12 in the provisional application), lines 18 to 21, and at the sixteenth page (labeled as page 14 in the provisional application), lines 2 to 4. These claims are therefore entitled to a priority date of April 1, 1999. Applicants submit herewith (as Exhibit A) an *In re* Katz Declaration signed by Leo E. Otterbein establishing that Lin. L. Mantell made no inventive contribution to the present

application. The Otterbein abstract reports the inventors' own work and was published less than one year before the April 1, 1999 priority date. It therefore is not prior art under any subsection of 35 U.S.C. §102 with respect to these claims.

With respect to amended claims 44 to 47, applicants respectfully traverse this rejection. The Otterbein abstract describes using carbon monoxide gas to protect against hyperoxic lung injury in rats. The Otterbein abstract does not disclose, or even suggest, using carbon monoxide to treat the specific disorders recited in claims 44, 45, 46 and 47, i.e., bronchitis, cystic fibrosis, pneumonia and interstitial lung disease, respectively. Since the Otterbein abstract does not describe or suggest such specific treatments, it neither anticipates nor render obvious claims 44 to 47.

For the reasons discussed above, applicants request that the rejection of claims 43 to 47, 50, 53, 62, 65, 67, 104 and 108 be reconsidered and withdrawn.

Claims 42 to 47, 50, 53, 62, 65, 67, 104 and 108 were also rejected under 35 U.S.C. §102 (f). The Office Action cites the Otterbein publication as alleged evidence that applicants did not invent the claimed subject matter. As discussed above, applicants submit herewith an *In re Katz* Declaration signed by Dr. Leo E. Otterbein establishing that Lin L. Mantell made no inventive contribution to the present application. Thus, applicants submit that the inventive entity (Drs. Augustine M.K. Choi and Leo E. Otterbein) recited for the present invention is complete and correct. Accordingly, applicants request that this rejection be reconsidered and withdrawn.

Claims 60, 61, 90 to 95, 100, 101, 116 and 117 were rejected as allegedly obvious over Maxwell et al. (*J. Pharmacol.*, 49:270-282 (1933)) in view of Campbell (*Brit. J. Exp. Path.*, 15(5):287-294 (1934)). Applicants respectfully traverse this rejection for the reasons below.

The Office Action states (at page 10, lines 7 to 19):

> In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references.

* * *

> The fact that a number of mice died due to carbon monoxide exposure is not sufficient to overcome the rejection as it is well within the skill of one of ordinary skill to use amount of carbon monoxide which are sublethal as evidenced by the Maxwell reference. Applicant argues that because Maxwell only shows retardation of growth and there are side effects that it would likely be unacceptable as clinical treatment in any animal, much less humans. However, the mere fact that there are adverse effects of treatment is not sufficient to preclude the clinical use of a drug. If this were true, then no drug, especially, such potent drugs as are currently used for treatment of cancers would not be used much less have been developed for use. Clearly, it is within the skill of one ordinary skill in the art, for example a physician, to modify doses depending on efficacy and toxicity.

Contrary to the Office Action's above-quoted assertions, applicants respectfully submit that they have, in fact, clearly addressed the previous Office Action's cited combination of references. Applicants were not simply arguing that neither reference, singly, rendered the presently claimed invention obvious, but were explaining that Maxwell and Cambell provided skilled practitioners with no motivation to combine these two references to arrive at a method of treating cancer by administering CO to a patient. In so arguing, applicants also made the point that both of the cited references actually teach away from using CO as a therapeutic agent.

Naturally, applicants began by discussing the shortcomings of Cambell and Maxwell individually and explained why each actually teaches away from using CO as a therapeutic agent. For example, applicants pointed out that Campbell reports that at the time the first wart appeared on a mouse, only 52% of the carbon monoxide-treated mice were still alive, compared to 77% of the air-breathing mice (page 290). According to Campbell (at page 290), "[t]his is to be expected as an effect of carbon monoxide." Applicants pointed out that a "treatment" that produces substantially more deaths at any time point than the condition being treated would likely not be viewed by skilled practitioners as a viable medical treatment. Thus, Campbell emphatically teaches away from using CO as a therapeutic agent.

With respect to Maxwell, applicants pointed out that this reference makes many negative statements about CO administration and its effects on the body (e.g., severe anoxia, weakness and prostration, etc.), and therefore cannot be said to have taught a clinically useful approach to

treating cancer. Applicants asserted that Maxwell certainly did not suggest investigating CO as a possible therapeutic agent for treatment of cancer, and that instead, one reading Maxwell would have been dissuaded from exploring such treatments. Thus, far from overcoming the teaching-away in Campbell, Maxwell makes the teaching-away even more pronounced.

Next, applicants explained that a skilled practitioner, having read Campbell and Maxwell, would have had no reason to expect such treatments to be clinically appropriate given the harmful effects described by these two references. Applicants concluded by explicitly stating their position that neither of the publications cited in the Office Action, singly or in combination, rendered the pending claims obvious.

In order to address a combination of references, one must first understand what each says individually, and then interpret what motivation (if any) and expectation of success (if any) one of extraordinary skill would derive from the combination. Applicants have made the case that both Campbell and Maxwell, taken individually or together, demonstrate that administration of CO is not clinically useful treatment for cancer. Asserting, as does the Office Action, that "it is within the skill of one of ordinary skill in the art, for example, a physician, to modify doses depending on efficacy and toxicity" does not mean that one would find in Campbell and Maxwell a motivation to try doing so, much less an expectation of success. Neither reference suggested that there might be a dose of CO high enough to retard the growth of a tumor, yet low enough not to produce the dangerous effects of CO poisoning. Indeed, Maxwell focused on CO because it produces anoxia, and Campbell studied it only because he surmised that one exposed to road dust would also be exposed to automobile exhaust containing CO. Furthermore, note that the references were published seventy years ago, and that no one since (other than the present inventors) has seriously investigated CO as a viable treatment for cancer. The teachings-away in these references were apparently quite convincing.

Accordingly, applicants have, in fact, thoroughly addressed the Office's cited combination of Campbell and Maxwell. Applicants submit that the Office Action has not established that the claims are obvious over this combination and therefore request that the present rejection be reconsidered and withdrawn.

CONCLUSION

Applicants submit that all claims are in condition for allowance, which action is requested. Enclosed is a check for $950 for the Petition for Extension of Time fee for a three-month extension. Please apply any other charges or any credits to Deposit Account No. 06-1050, referencing Attorney Docket Number 13681-003002.

Respectfully submitted,

Date: 9/1/04

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